Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendments, claims 1, 3-10, 13, and 24-37 are pending in the application, with 1, 8, 9, 10, and 31 being the independent claims. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Priority

The Examiner contends that Applicants are not entitled to the benefit of priority for claims directed to SEQ ID NOS:1-3 because the sequences, as amended, do not appear in the priority applications, and there is insufficient proof that the deposited clones are the same as those in the priority documents. *Paper No. 16*, pages 2-3.

Applicants maintain that the amendments to the Sequence Listing do not introduce new matter because the amendments reflect the correct nucleotide and amino acid sequences contained in the deposited clones, ATCC Deposit Nos. 209933, 209934 and 98809. The clones contained in ATCC Deposit Nos. 209933 and 209934 were deposited on June 16, 1998 (prior to the filing of the first provisional application) and the clone contained in ATCC Deposit No. 98809 was deposited on July 10, 1998 (prior to the filing of the second provisional application). See the specification at page 16, lines 7-10. Therefore, since the correct sequences were inherent to the deposited clones at the

time the application was filed, and the deposit information formed part of the original specification, we believe that no new matter was introduced by the amendment to correct sequence errors. Accordingly, it is believed that Applicants are entitled to the June 25, 1998 filing date for sequences contained within ATCC Deposit Nos. 209933 and 209934 and the July 24, 1998 filing date for the sequence contained within ATCC Deposit No. 98809.

There is a line of chemical case law where applicants have been permitted to amend the specification to correct the formula of a chemical compound after an application's filing date provided that it had been demonstrated that one of skill in the art would have appreciated that the applicant was in possession of the compound itself at the time of filing. The rationale is that the formula is an inherent property of the compound and thus amending the specification to correct the formula is not new matter. See *In re Nathan*, 140 U.S.P.Q. 601, 604 (C.C.P.A. 1964). *Accord Kennecott Corp. v. Kyocera Int'l, Inc.*, 5 U.S.P.Q.2d 1194, 1198 (Fed. Cir. 1987), *cert. denied*, 486 U.S. 1008 (1988) ("The disclosure in a subsequent patent application of an inherent property of a product does not deprive that product of the benefit of the earlier filing date.").

Further, Applicants direct the Examiner's attention to the Federal Circuit's decision in *Enzo Biochem, Inc., v. Gen-Probe, Inc.*, wherein the court held that reference in a patent specification to a deposit in a public depository of a nucleotide sequence, which makes its contents accessible to the public when it is not otherwise available in written form, constitutes an adequate description of the deposited material sufficient to comply with the written description requirement of § 112. *Enzo Biochem, Inc., v. Gen-Probe, Inc.*, 323 F.3d 956, 970 (Fed. Cir. 2002). Because the question of priority turns on whether there is adequate written description support for the claimed invention in the

priority document to satisfy § 112, first paragraph, and the Federal Circuit has held that reference to a deposited polynucleotide satisfies the requirement, it follows that claims directed to a deposited polynucleotide are entitled to claim the benefit of the priority document.

The MPEP is also instructive on whether amendments to the sequence listing can be made if the specification references a polynucleotide deposit.

> With respect to the correction of sequencing errors in applications disclosing nucleic acid and/or amino acid sequences, it is well known that sequencing errors are a common problem in molecular biology. If an application as filed includes sequence information and references a deposit of the sequenced material made in accordance with the requirements of 37 CFR 1.801 *et seq.*, amendment may be permissible. . . Corrections of minor errors in the sequence may be possible based on the argument that one of skill in the art would have resequenced the deposited material and would have immediately recognized the minor error.

MPEP, February 2003, at 2100-162 (citations omitted). Thus, the whole weight of authority supports Applicants' position that amendments to the sequence listing can be made when reference is made to a deposited polynucleotide.

Applicants sequence amendments in coding sequence were minimal, numbering six nucleotides for mouse Dnmt3a, two nucleotides for mouse Dnmt3b, and six nucleotides for human DNMT3A. Because the instant polynucleotide sequences as filed are easily distinguishable from other sequences, and Applicants' amendments to the sequences were minimal, the artisan would instantly comprehend that the resequenced polynucleotides were one in the same as the polynucleotides as described in the application as filed. Thus, as instructed by the MPEP, correction of the sequence listing by amendment is proper.

Accordingly, Applicants respectfully request that the Examiner acknowledge the Applicants' claim to priority.

Objections to the Drawings

The Examiner objected to the drawings, referring to the reasons cited on form PTO 948 purportedly attached to the current Office Action. The Examiner further objected that a clean copy did not accompany a marked up copy of the Figures. *Paper No. 16* at page 3.

Applicants respectfully request that the Examiner forward form PTO 948 to the Applicants, as this form was not attached to the current Office Action[1]. Applicants note that the clean copies of Figures 1A, 1B-1, IC, 2A, 2B, 2C and 3A, as amended, were submitted as Formal Drawings in connection with the Amendment and Reply filed on June 16, 2003. Applicants attach hereto as **EXHIBIT A** the date stamped postcard and copies of the drawings as filed in support thereof. Withdrawal or clarification of this objection is respectfully requested.

Objections to the Specification

The Examiner objected to Figures 1A, 1B-1, 1C, 2A, 2B, 2C, 3A and 3B under 35 U.S.C. §132 as allegedly introducing new matter into the disclosure. The Examiner has required the Applicants to cancel the new matter in reply to the Office Action. *Paper No. 16,* page 5. The Examiner further objected that clean copies did not accompany the marked up copies.

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[1]Applicants note that a PTO 948 form was attached to Paper No. 12.

As described above under "***Priority,***" the polynucleotides shown in corrected Figures 1A, 1B-1, IC, 2A, 2B, 2C, 3A and 3B have adequate 35 U.S.C. § 112, first paragraph support in the priority documents by reference to the deposits. Thus, no new matter was added to the disclosure by submission of the corrected Figures. As described above, Applicants note that clean copies were submitted as Formal Drawings to the PTO Draftsman. Accordingly, Applicants respectfully request that the Examiner withdraw the objection.

Objections to the Claims

The Examiner objected to claim 1(f) because the term polynucleotide was misspelled. *Paper No. 16*, page 5, last paragraph. Applicants have corrected the error. Accordingly, Applicants respectfully request that the Examiner withdraw the objection.

Rejections Under 35 U.S.C. § 112, First Paragraph (written description)

The Examiner rejected claims 8 and 10 under 35 U.S.C. §112, first paragraph as allegedly containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention. *Paper No. 16*, page 6. Applicants respectfully traverse this written description/new matter rejection.

An applicant satisfies the written description requirement when the disclosure of the application relied upon "reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter." *Ralston Purina Co. v. Far-Mar-Co., Inc.*, 772 F.2d 1570, 1575, 227 USPQ 177, 179 (Fed. Cir. 1985) (quoting *In re Kaslow*, 707 F.2d 1366, 1375, 217 USPQ 1089, 1096 (Fed. Cir. 1983). Applicant

demonstrates possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.* 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1996 (Fed Cir. 1997). Further, what is conventional or well known to one of ordinary skill in the art need not be disclosed in detail. *Hybritech Inc. v. Monoclonal Antibodies, Inc.* 802 F.2d at 1384, 231 USPQ at 94. The description need not be in *ipsis verbis* to be sufficient. *Martin v. Johnson*, 454 F.2d 746, 751, 172 USPQ 391, 395 (CCPA 1972).

Applicants respectfully believe that the Examiner's rejection of claims 8 and 10 is improper. The Examiner does not provide any reasoning for the rejection, merely stating that "[l]ines 7-25 of page 21 do not support that Applicants contemplated contiguous nucleotide of SEQ ID NO:1 and 3 consisting of discrete fragments of 50 and 100 nucleotide length, respectively at the time of filing." *Paper No. 16*, page 6.

The Examiner has not established a *prima facie* case of lack of written description because the Examiner has not provided any reasoning why persons skilled in the art would not recognize that the disclosure describes fragments of 50 and 100 nucleotides in length of SEQ ID NOS:1 and 3. The MPEP is instructive in this regard, providing:

> [i]f applicant amends the claims and points out where and/or how the originally filed disclosure supports the amendment(s), and the examiner finds that the disclosure does not reasonably convey that the inventor had possession of the subject matter of the amendment at the time of filing of the application, the examiner has the initial burden of presenting evidence or reasoning to explain why persons skilled in the art would not recognize in the disclosure a description of the invention defined by the claims.

MPEP, February 2003, at § 2163.04. Thus, the Examiner's rejection is improper.

Contrary to the Examiner's statement, Applicants contend that the specification contains a written description of the claimed fragments of SEQ ID NOS:1 and 3. Applicants respectfully direct the Examiner to the specification:

> Generally, polynucleotide fragments of the invention may be defined algebraically in the following way: (a) for SEQ ID NO:1, as 15 + N, wherein N equals zero or any positive integer up to 4176; (b) for SEQ ID NO:2, as 15 + N, wherein N equals zero or any positive integer up to 4180; and (c) for SEQ ID NO:3, as 15 + N, wherein N equals zero or any positive integer up to 4401.

Specification, page 21, lines 17-25. The specification makes clear that Applicants were in possession of polynucleotide fragments defined algebraically as 15 + N, wherein N equals zero or any positive integer up to 4176, 4180, or 4401 for SEQ ID NOS:1, 2, or 3 respectively. Thus, the specification expressly discloses discrete fragments that can be anywhere from 15 to 4191 nucleotides in length for SEQ ID NO:1 and from 15 to 4416 nucleotides in length for SEQ ID NO:3. In light of such disclosure, one skilled in the art would instantly comprehend that the specification describes the discrete fragments encompassed by the range, and that the 50 and 100 nucleotide fragments of SEQ ID NOS:1 and 3 are but two species of the genus described. Consequently, it cannot be maintained that claims directed to said fragments fail to meet the written description requirement.

Based on the forgoing, Applicants respectfully request that the Examiner reconsider and withdraw the written description rejection of claims 8 and 10 under 35 U.S.C. § 112, first paragraph.

The Examiner also rejected claim 24 for alleged lack of written description. The Examiner, however, did not provide any explanation or rationale as to why claim 24

should be rejected for lack of written description. Accordingly, the rejection is incomplete and Applicants cannot be responsive. Withdrawal or clarification of the rejection of claim 24 is respectfully requested.

Rejections Under 35 U.S.C. § 112, First Paragraph (enablement)

The Examiner rejected claims 1, 3-10, and 24-37 under 35 U.S.C. §112, first paragraph, because the specification does not reasonably provide enablement commensurate with the scope of the claimed invention. *Paper No. 16*, pages 7-8. Applicants respectfully traverse this ground of rejection.

In order for a claim to be enabled, the specification must teach one of ordinary skill in the art how to make and use the invention without undue experimentation. The factors that can be considered in determining whether an amount of experimentation is undue have been set forth in *In re Wands*, 858 F.2d 731, 737, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988). Among these factors are: the amount of experimentation involved, the guidance provided by the specification, the presence of working examples, the amount of pertinent literature and the level of skill in the art. The test for undue experimentation is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine. *Id.*

While the predictability of the art can be considered in determining whether an amount of experimentation is undue, mere unpredictability of the result of the experiment is not a consideration. Indeed, in *In re Angstadt*, the Court of Custom and Patent Appeals has specifically cautioned that the unpredictability of the result of an experiment is not a basis to conclude that the amount of experimentation is undue:

> If to fulfill the requirements of 112, first paragraph, an applicant's disclosure must provide guidance which will enable one skilled in the art to determine, with reasonable certainty before performing the reaction whether the claimed product will be obtained, . . . then all "experimentation" is "undue" since the term "experimentation" implies that the success of the particular activity is uncertain. Such a proposition is contrary to the basic policy of the Patent Act.

537 F.2d at 503, 190 U.S.P.Q. at 219 (emphasis in the original).

As a preliminary matter, Applicants would like to point out that the Examiner has misrepresented a statement made in Applicants' previous Amendment and Reply. In the current Office Action, the Examiner states: "Applicants attest the approach by the Lazar reference cited by the Examiner differs from a potential infringer of Applicants' claims." *Paper No. 16*, page 7. Applicants respectfully qualify the Examiner's remarks by directing the Examiner to the sentence in the Amendment and Reply to which the Examiner relies:

> Such an approach contrasts sharply with that of a potential infringer of Applicants' claims that is motivated to make substitutions to Applicants' sequence to obtain sequences that are at least 95% identical that maintained *de novo* methyl transferase activity.

Amendment and Reply dated June 16, 2003, page 15. Applicants further direct the Examiner to the following:

> On the other hand, if a potential infringer were interested in making mutations that abrogated biological activity of the *de novo* methyltransferases, Applicants sequence alignments provide guidance on which of the residues would be most appropriate to mutate.

Id. Thus, the Applicants do not take the position that a potential infringer would only be interested in making mutants that maintain activity. To the extent that a potential

infringer makes mutants with the goal of maintaining protein activity, the infringer's approach differs from that of Lazar *et al.*

The Examiner further argues that the "Applicants' specification does not provide sufficient guidance in the identification of which amino acid residues of the claimed polynucloetides are tolerant of modification and which are conserved and detailed knowledge of the ways in which the protein's structure relates to its function" and that "[t]he specification provides essentially no guidance as to which of the infinite possible choices is likely to be successful." *Paper No. 16*, pages 7-8. The Examiner further argues that "the unidentified subfragments of SEQ ID NO:1-4 are more than likely not to encode full-length polypeptides capable of *in vitro* methylation at the C5 position in DNA." *Id.* Applicants respectfully disagree with the Examiner.

Applicants assert that methods of making mutants are routine in the art. The fact that tens of thousands of scientific publications report various mutant polypeptides evidences that mutagenesis techniques are routine. While it is impossible to predict with absolute certainty whether a given mutant will have wild-type activity, the construction and testing of such a mutant is routine. It is known in the art that amino acid replacements in many parts of a polypeptide chain can be made without seriously modifying the activity of the polypeptide. In support thereof, Applicants submit herewith **EXHIBIT B**, which provides in relevant part:

> [i]n fact, evidence now indicates that amino acid replacements in many parts of a polypeptide can occur without seriously modifying catalytic activity.

EXHIBIT B; Watson *et al.* (1987), *Molecular Biology of the Gene, 4th Edition*, Benjamin/Cummings Publishing Co. (Menlo Park, CA), pages 226-227. Thus, it cannot be established that construction of a mutant polypeptide is undue.

One of the most common mutagenesis methods to relate structure to function is alanine scanning mutagenesis. In alanine scanning mutagenesis, the artisan mutates wild-type residues to alanines over a range of residues in order to determine which residues are important for the protein's biological activity. Alanine is selected as the substituted amino acid because it is a relatively neutral amino acid that is unlikely to affect a protein's biological activity except in positions that are critical for activity. Using this technique, the artisan can "scan" randomly for mutants that affect a protein's activity or more commonly, the artisan scans a region of interest based on homology to a known consensus sequence or known domain that harbors protein activity. Using either approach, the artisan will obtain mutants that have a range of activities. Applicants submit herewith a publication by Kristensen *et al. J. Biol. Chem. 272*:12978-83 (1997) as **EXHIBIT C**. Kristensen *et al.* report binding experiments of mutant insulin prepared by alanine scanning mutagenesis. Despite the fact that insulin is a small protein of 51 amino acids comprising two separate polypeptide chains, Kristensen *et al.* generate a large number of mutants that bind insulin receptor with an affinity at least as high as that of wild-type insulin. Applicants respectfully direct the Examiner's attention to the following:

> In contrast to the disruptive mutations there were a number of alanine substitutions that did not alter affinity for the receptor, and at least three of the alanine analogs even showed an increase in receptor affinity.

EXHIBIT C, page 12980. Thus, even using a *random* scanning approach, Kristensen *et al.* was able to make functional mutants of a very small protein. Because the instant polypeptides are much larger than insulin, the artisan would have a much higher probability of success in constructing mutants with wild-type activity using the approach

of Kristensen *et al.* However, if the artisan were interested in creating functional mutants, the artisan would likely not make random mutations to alanine. Rather, the artisan would make more conservative amino acid substitutions, as the instant specification teaches:

> [p]referred variants are those that vary from the reference by conservative amino acid substitutions, *i.e.*, those that substitute a residue with another of like characteristics. Typical substitutions are among Ala, Val, Leu and Ile; among Ser and Thr; among the acidic residues Asp and Glu; among Asn and Gln; and among the basic residues Lys and Arg, or aromatic residues Phe and Tyr.

Specification, page 34, lines 9-14. Using the approach as set forth by the specification, the artisan would have an even higher probability of success than the random scanning approach because such substitutions are less likely to perturb the protein's structure and function.

While the Examiner objects that the specification does not provide sufficient guidance in the identification of which amino acid residues of the claimed polynucleotides are tolerant of modification and which are conserved, it is clear based on the teachings of Kristinsen *et al.* that such a showing is not required in order to arrive at functional mutants using, for example, a routine alanine scanning mutagenesis approach. However, as described in the previous Amendment and Reply, Applicants disclosure does provide *extensive guidance* to the artisan as to which amino acids are the best candidates to mutate based on sequence conservation.

Applicants direct the Examiner's attention to FIG 3A-1 which shows an amino acid alignment of Dnmt3a and Dnmt3b. It is clear from the alignment that Dnmt3a and Dnmt3b are highly related polypeptides and display extensive regions of identity/similarity. Based on such disclosure, the skilled artisan would be guided to

make substitutions of residues in one protein to conserved residues in the other. For example, the following conserved substitutions can be made to Dnmt3a:

Dnmt3a residue (position)	Dnmt3b residue (position)	Mutate Dnmt3a residue to:
Q77	**E10**	**E**
D78	**E11**	**E**
L84	**I21**	**I**
L85	**I22**	**I**
K150	**R105**	**R**
L184	**I139**	**I**
Y192	**H147**	**H**
Y193	**H148**	**H**
I194	**V149**	**V**

Thus, the specification provides sufficient guidance in the identification of which amino acid residues of the claimed polynucloetides are tolerant of modification and which are conserved. The specification also provides in Example 4 a method for screening proteins for DNA cytosine methyltransferase activity. Therefore, the specification teaches one skilled in the art how to make and use the claimed polynucleotides.

In regard to the unidentified subfragments of SEQ ID NOS:1-3 of claims 8-10, Applicants maintain that the claim does not require that the nucleotide fragments encode proteins or peptides that have DNA cytosine methyltransferase activity. Rather, the specification discloses that the DNA fragments may be useful as probes or primers for screening or amplifying Dnmt3. Polynucleotide fragments can also be used for making antisense oligonucleotides to inhibit Dnmt3 expression. Therefore, it is improper for the Examiner to reject the claims solely on the basis that the nucleotide fragments may not encode functional polypeptides.

Based on the foregoing, Applicants respectfully request that the Examiner reconsider and withdraw the enablement rejection under 35 U.S.C. § 112, first paragraph.

Rejections Under 35 U.S.C. § 102

First, the Examiner rejected claims 1, 3, 4, 8, 9, 24-26, 29-33, 36, and 37 under 35 U.S.C. 102(b) as allegedly anticipated by Okano *et al.* as evidenced by Accession numbers AF068625, AF068626 and AF068627. *Paper No. 16*, page 8. Second, the Examiner rejected claims 1, 3, 4, 8, 10, 24, 27-31, and 34-37 under 35 U.S.C. 102(b) as allegedly anticipated by Xie *et al.* as evidenced by Accession number AF067972. *Id.*, page 9. Applicants traverse these rejections as they may be applied to the pending claims.

At the outset, Applicants respectfully point out to the Examiner that claims 31-37 are directed to, *inter alia*, polynucleotides contained in ATCC Deposit Nos. 209933, 209934, 98809 and 326637. Nowhere in these claims is the sequence identifier (SEQ ID NO) recited. Thus, even if the Applicants' effective filing date for the revised SEQ ID NOS:1, 2 and 3 is July 13, 2001, which Applicants do not concede for the reasons stated above under "***Priority***," it does not follow that Okano *et al.* and Xie *et al.* are prior art under 35 U.S.C. §102(b) to claims 31-37.

Similarly, Applicants also object to the Examiner's rejection of claim 28, which is directed to an isolated nucleic acid molecule encoding a polypeptide comprising amino acids from about 1-853 in SEQ ID NO:8. Applicants respectfully point out to the Examiner that the polynucleotide encoding SEQ ID NO:8 has not been amended. Thus, it cannot be disputed that SEQ ID NO:4 is entitled to its earliest priority date.

Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejection.

For the reasons set forth above under "***Priority***," Applicants maintain that they are entitled to the June 25, 1998 filing date for sequences contained within ATCC Deposit Nos. 209933 and 209934 and the July 24, 1998 filing date for the sequences contained within ATCC Deposit No. 98809. Thus, the Okano *et al.* and Xie *et al.* publications are not prior art under § 102.

The Examiner also rejected claim 13 under 35 U.S.C. 102(e) as allegedly anticipated by U.S. Patent No. 6,492,168 (the '168 patent). Applicants traverse this rejection as it may be applied to the pending claims.

The Examiner contends that "U.S. Patent #6,492,168 discloses a nucleic acid sequence that is complementary to any one of SEQ ID NO:5-8, which is capable of contacting DNA allowing for a method of utilizing an expressed novel methyltransferase (M.CviPI) to methylate GpC *in vitro*, see column 18, lines 31-43 and column 20, lines 60-67." *Paper No. 16*, page 11.

Applicants respectfully disagree with the Examiner that the '168 patent discloses a nucleic acid sequence complementary to any one of SEQ ID NOS:5-8. First, as a practical matter, SEQ ID NOS:5-8 are *polypeptide* sequences, and as such, cannot be complementary to *polynucleotide* sequences. One skilled in the art appreciates that a polynucleotide molecule is "complementary" to another polynucleotide molecule if it forms Watson-Crick base-pairs (e.g., A-T and G-C) at each nucleotide position. Thus, only polynucleotide molecules can be complementary to other polynucleotide molecules as understood by the one of skill in the art. Second, the '168 patent does not disclose *any* polynucleotide molecule as claimed in claim 1, or *any* polynucleotide molecule

complementary thereto encoding a polypeptide represented by any one of SEQ ID NOS:5-8. If the Examiner refuses to withdraw the rejection, Applicants request that the Examiner specifically point to a polynucleotide sequence in the '168 patent that is the same or complementary to any polynucleotide sequence of claim 1. Because no such sequence is disclosed in the '168 patent, the rejection cannot be maintained.

Based on the foregoing, Applicants respectfully request that the Examiner reconsider and withdraw the rejections under 35 U.S.C. §102.

Rejections Under 35 U.S.C. § 103

The Examiner rejected claims 1, 3-10, 24-26, 29-33, 36 and 37 under 35 U.S.C. §103(a) as allegedly being unpatentable over Okano *et al.* as evidenced by Accession numbers AF068625 and Xie *et al.* as evidenced by Accession number AF067972, in view of Ausubel *et al.* Applicants respectfully traverse this ground of rejection.

For the reasons set forth above under "***Priority***," Applicants maintain that they are entitled to the June 25, 1998 filing date for sequences contained within ATCC Deposit Nos. 209933 and 209934 and the July 24, 1998 filing date for the sequences contained within ATCC Deposit No. 98809. Thus, the Okano *et al.* and Xie *et al.* publications are not proper prior art under 35 U.S.C. § 103.

Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejection.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

Karen R. Markowicz

Karen R. Markowicz
Agent for Applicants
Registration No. 36,351

Date: 12/9/03

1100 New York Avenue, N.W.
Washington, D.C. 20005-3934
(202) 371-2600